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Inventors: Siegel et al.  
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#### REMARKS

Claims 1-10 are pending in the instant application. Claim 1-10 have been rejected. Claims 1 and 4 have been amended. Support for these amendments is provided in the specification at page 9, lines 7-9, page 13, lines 11-20, and page 14, lines 8 and 26-28. No new matter is added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

#### I. Rejection of Claims 1-3 under 35 U.S.C. 102(b) and 7-10 under 35 U.S.C. 103(a)

The Examiner has maintained the rejection of claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Kino et al. (WO 94/10982, English Abstract). The Examiner suggests that Kino discloses an implantable system that comprises haloperidol and lactic acid/glycolic acid copolymer, thus meeting the limitations of the claims.

The Examiner has also maintained the rejection of claims 1 through 3 under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (J. Controlled Release, 1988, 203-212). The Examiner suggests that Cheng discloses a delivery system that comprises haloperidol and 50:50 lactide-glycolide copolymer and use of haloperidol in the treatment of schizophrenia. Further, the Examiner suggests that Cheng teaches loading haloperidol onto lactide-

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glycolide copolymer in the presence of the organic solvent, dichloromethane, emulsifies the mixture and the solvent is evaporated off to produce microspheres. Thus, the Examiner suggests that Cheng meets the limitations of the claims.

With respect to the phrase surgically implantable in claim 1, the Examiner suggests that this is a future intended use and carries no patentable weight in a composition claim.

Further, the Examiner suggests that claims 7-10, which depend from claim 1, are obvious over teachings of Cheng et al.

Applicants respectfully traverse these rejections.

At the outset, Applicants respectfully disagree with the Examiner's assertion that "surgically implantable" is merely an intended use with no patentable weight. Surgically implantable is also indicative of the structure and/or size of the drug delivery device of the present invention. As made clear in the teachings throughout the specification, the device of the present invention has a structure which permits its surgical implantation through an incision in the skin. See teachings, for example at pages 13 and 14. Also see the Background Section at page 4 providing examples of other well-known surgically implantable drug delivery devices. Clearly, the phrase surgically implantable, when read in light of teachings of

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the specification provides knowledge to the skilled artisan of the structure of the present invention. Accordingly, the Examiner's assertion that no patentable weight is given to this phrase is contrary to MPEP 2111.02 and established case law stating that during examination, statements in the claims, including statements in the preamble, regarding the purpose or intended use of the claim invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or in the case of process claims, manipulative differences) between the claimed invention and the prior art. If so, the recitation serves to limit the claim. See MPEP 2111.02 at page 2100-52 and *In re Otto* 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963).

Further, the structure of the surgically implantable drug delivery device of the present invention is very different from the structure of the sustained release microspheres described by Kino and Cheng. In particular, sustained release microspheres such as taught by Kino and Cheng are microscopic. In EP 0 669 128 B1 (which corresponds to WO 94/10982) Kino teaches their size to range from about 0.5 to about 400  $\mu\text{m}$ , more preferably from about 0.5 to about 200  $\mu\text{m}$ , as an average particle size (see EP 0669 128 B1 at col. 4-5, paragraph [0019]). Cheng et al. teach the size of their microspheres to range in size from

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0.43 to 14.76  $\mu\text{m}$ . Accordingly, administration of sufficient drug to achieve steady state concentrations and the desired pharmacological activity requires suspension of thousands of these tiny particles into an injectable formulation.

Further, Kino states that their sustained release microsphere can exhibit a desired pharmacological effect, where a long-term administration is necessary, by injecting every 1 to 8 weeks while Cheng et al. state the time of 50% drug release ( $T_{50\%}$ ) to be around 55 days. Cheng et al. also teaches that the maximum theoretical loading of haloperidol into their microspheres is around 10%. See Cheng et al. first column of page 208.

In contrast, the drug delivery device system of the present invention comprises a single, individual biodegradable polymer-haloperidol implant with 20 to 40% haloperidol. This single implant is not microscopic, but rather is sized to be implanted surgically. This single implant contains 2 to 4-fold higher haloperidol concentrations than the maximum concentration taught to be loaded into the microspheres of Cheng. Further, this single, individual implant delivers steady state concentrations, a concentration understood by the skilled artisan to produce a desired pharmacological effect, of haloperidol to the patient for 5 months or more. Clearly, the ability of the drug delivery system of the present

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invention to extend drug delivery time by at least 90 days and 40 days as compared to the microsphere preparations taught by Kino and Cheng, respectively, is indicative of yet another structural difference between the drug delivery system of the present invention and the microsphere suspension taught by Kino and Cheng.

In an earnest effort to advance the prosecution of this case and to clearly distinguish structurally the drug delivery system of the present invention from sustained release microspheres such as taught by Kino and Cheng, Applicants have amended claim 1 to state that the surgically implantable drug delivery system consists essentially of biodegradable polymer or copolymer and 20 to 40% haloperidol fabricated into an individual, surgically implantable implant via solvent casting and compression molding at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more and is removable from the patient in the event the patient exhibits unwanted side effects following implantation. Support for these amendments is provided in the specification at page 9, lines 7-9, page 13, lines 11-20, and page 14, lines 8 and 26-28.

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Since neither Kino nor Cheng teach an individual implant of biodegradable polymer and 20 to 40% haloperidol sized to be surgically implanted and which delivers steady state concentration of haloperidol to a patient for 5 months or more, these references cannot anticipate the claims as amended.

Withdrawal of these rejections under 35 U.S.C. 102(b) is therefore respectfully requested.

Further, with respect to the rejection of dependent claims 7-10 under 35 U.S.C. 103(a) as being unpatentable of Cheng et al., MPEP 2143.03 states that if an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. Also see *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). MPEP 2143.03 further states that to establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. "All the words in a claim must be considered in judging the patentability of the claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

As discussed in detail above, Cheng does not teach a drug delivery system consisting essentially of biodegradable polymer or copolymer and 20 to 40% haloperidol fabricated into an individual, surgically implantable implant which delivers steady state concentrations of haloperidol to the

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patient for 5 months or more. Nor is there any suggestion of such a drug delivery system in Cheng et al. Accordingly, this reference does not teach or suggest all the limitations of the claimed invention and cannot render obvious claim 1 or claims 7-10 depending therefrom.

Withdrawal of this rejection under 35 U.S.C. 103(a) is therefore respectfully requested.

**II. Rejection of Claims 1-6 under 35 U.S.C. 102(e) and  
Rejection of Claims 7-10 under 35 U.S.C. 103(a)**

The rejection of claims 1-6 under 35 U.S.C. 102(e) as being anticipated by Brodbeck et al. (U.S. Patent 6,130,200) has been maintained. The Examiner suggests that Brodbeck et al. disclose methods and compositions for systemically or locally administering by implantation a beneficial agent to a subject and includes haloperidol as an example of a beneficial agent. The Examiner suggests that the compositions of Brodbeck comprise 50:50 poly(lactide-co-glycolide) copolymers and, in the preparation, solvents are involved. Therefore, the Examiner suggests that Brodbeck et al. meets the limitations of the claims.

Claims 7-10, which depend from claim 1, have also been rejected under 35 U.S.C. 103(a) as being unpatentable over Brodbeck et al. (U.S. Patent 6,130,200).

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Applicants respectfully traverse these rejections.

Solvent are not merely "involved" in the preparation of the compositions of Brodbeck et al., but rather are a required element which remains in the gel preparation upon administration. See specifically the Abstract wherein it is taught that the compositions include a biocompatible polymer, a biocompatible solvent having low water miscibility that forms a viscous gel with the polymer and limits water uptake by the implant, and a beneficial agent. Also see teachings col. 8, lines 36-53, col. 10, lines 40-64, col. 11, line 50 through col. 14, line 37, and col. 17, line 51 through col. 18, line 9, wherein the requirement for a biocompatible solvent in the gel preparations is described in more detail.

In contrast, claim 1 and claims dependent therefrom are drawn to a drug delivery system **consisting essentially of** biodegradable polymer or copolymer and 20 to 40% haloperidol and claim 4 specifically states in step (b) that solvent casting is performed on the haloperidol and biodegradable polymer solution to produce a completely dry haloperidol-polymer material. Teachings of the specification at page 8, line 27, through page 9, line 6 also make clear that any solvent used in preparation of the implant of the drug delivery system is evaporated by solvent casting during

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preparation of the implant. Thus, both method claims 4 through 6 and compositions claims 1-3 of the instant application are clearly drawn to a drug delivery system that does not contain the essential biocompatible solvent in the viscous gels of Brodbeck.

MPEP 2111.03 defines the transitional phrase "consisting essentially" of to limit the scope of the claim to the specified materials or steps and those that do not materially affect the basic and novel characteristics of the claimed invention. Clearly interpreting the scope of these claims to be inclusive of a solvent, when the claims specify the composition to be produced by solvent casting, a step explicitly taught in the specification and stated in claim 4 to produce a completely dry haloperidol-polymer material, is improper.

Elimination of the biocompatible solvent required by Brodbeck renders the instant claimed composition of claims 1-3 structurally different from the compositions taught by Brodbeck.

Further, inclusion of a solvent casting step to produce a completely dry haloperidol-polymer material in the instant claimed process of claim 4 clearly distinguishes method claims 4-6 from methods for production of the solvent containing gels taught by Brodbeck.

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In addition, Brodbeck teaches at col. 22, lines 9-10 that their viscous gels release beneficial agent for periods from about 7 to about 90 days. In contrast, the drug delivery system of the present invention is stated in the claims to deliver steady state concentrations of haloperidol to the patient for 5 months or more. Clearly, the ability of the drug delivery system of the present invention to extend drug delivery time by at least 50 days as compared to the solvent containing gel formulation of Brodbeck is indicative of yet another structural difference between the drug delivery system of the present invention and the gel formulation of Brodbeck.

Withdrawal of this rejection under 35 U.S.C. 102(e) is therefore respectfully requested.

Further, with respect to the rejection of dependent claims 7-10 under 35 U.S.C. 103(a) as being unpatentable of Brodbeck et al., MPEP 2143.03 states that if an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. Also see In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). MPEP 2143.03 further states that to establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. "All the words in a claim must be considered in judging the patentability of the

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claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

As discussed in detail above, Brodbeck et al. does not teach a drug delivery system consisting essentially of biodegradable polymer or copolymer and 20 to 40% haloperidol fabricated into an individual, surgically implantable implant which delivers steady state concentrations of haloperidol to the patient for 5 months or more. Nor is there any suggestion of such a drug delivery system (which does not contain as an essential element a biocompatible solvent) in Brodbeck et al. Any suggestion to exclude the biocompatible solvent from Brodbeck et al. would change its principle of operation and thus would be improper in accordance with MPEP 2143.02. Accordingly, this reference does not teach or suggest all the limitations of the claimed invention and cannot render obvious claim 1 or claims 7-10 depending therefrom.

Withdrawal of this rejection under 35 U.S.C. 103(a) is therefore respectfully requested.

### III. Rejection of Claims 4-6 under 35 U.S.C. 103(a)

Claims 4-10 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (J. Controlled Release, 1988 203-212).

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The rejection of claims 7-10 under 35 U.S.C. 103(a) is overcome by arguments presented in Section I, supra.

With respect to claims 4-6, the Examiner acknowledges that Cheng discloses a method of preparing microspheres by a process of emulsification-solvent evaporation. The Examiner suggests that the difference between Cheng and the instant claims is that Cheng does not specifically state that the composition is formulated as an implant. However, the Examiner suggests that Cheng discloses that the composition can be implanted. Thus, the Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare haloperidol-poly(lactide-co-glycolide)copolymer compositions. Further, the Examiner suggest that one having ordinary skill in the art would have been motivated to formulate the composition into an implant with the expectation of improving the degree of compliance and more predictable absorption.

Applicants respectfully traverse this rejection.

At the outset Applicants respectfully disagree with the Examiner's characterization of the single difference between Cheng and the invention of claims 4-6 being that Cheng does not "specifically state that the composition is formulated as an implant." Claims 4 through 6 are drawn to a method of producing an implant by dissolving haloperidol and a

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biodegradable polymer in acetone; solvent casting the haloperidol and biodegradable polymer solution to produce a completely dry haloperidol-polymer material; and molding under compression the dry haloperidol-polymer material at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold. No where does Cheng et al. teach or suggest molding under compression dry haloperidol-polymer material at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for an implant.

Accordingly, since this reference does not teach this step it cannot render obvious the claimed process. See MPEP 2143 which requires that all claim limitations be taught or suggested to establish prima facie obviousness.

Further, claim 4 has been amended in accordance with teachings at page 14, lines 8 and 26-28 to state that the process produces an individual, surgically implantable implant. This individual implant is completely different structurally from the suspension of thousands of tiny microscopic microspheres as taught by Cheng et al. Claim 4 has also been amended in accordance with teachings at page 13, lines 11-20, to state that the implant delivers steady state concentrations of haloperidol to the patient for 5 months or more. In contrast, the time for 50% drug release

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(T<sub>50%</sub>) of the microsphere formulations of Cheng et al. is around 55 days. The functional ability to extend the time of drug release by at least 40 days is indicative of yet a further structural difference between the implant produced in the instant claimed invention as compared to the microsphere formulations of Cheng et al.

MPEP 2116.01 is clear; All limitations of a claim must be considered when weighing the differences between the claimed invention and the prior art in determining the obviousness of a process or method claim. Thus, proper claim construction requires treating language in a process claim which recites the making and using of a nonobvious product as a material limitation. As discussed in detail in Section I, supra, the product made by the process of claim 4 is nonobvious over teachings of Cheng et al. Thus, in accordance with MPEP 2116.01, the process of claim 4 is also nonobvious.

Withdrawal of this rejection is therefore respectfully requested.

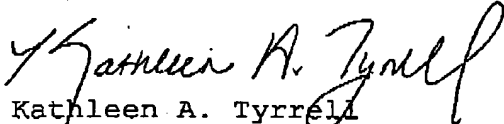
#### IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.

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Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

  
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